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CHAPTER 1

Geoepidemiology of Sarcoidosis

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INTRODUCTION

Sarcoidosis, a systemic disease of unknown etiology characterized by the development of noncaseating epitheloid cell granulomas, often affects young adults aged between 20 and 50 years.[1] Sarcoidosis is a systemic disease with a heterogeneous clinical presentation, although clearly dominated by thoracic involvement. Epidemiologically, sarcoidosis is a rare disease with a significant influence of ethnicity and environmental factors that play a key role in the phenotypic expression of sarcoidosis[2]; notably, the three organs most frequently affected (the lungs, skin, and eyes) are in direct contact with the external environment.[3]

The rarity of sarcoidosis, together with the key role of ethnic and geoepidemiological factors, means that the larger the population analyzed, the better the characterization of clinical expression, and the more likely the findings will reflect the real population affected by the disease. Big data–driven research is a key instrument that may help provide a high-definition picture of infrequent and heterogeneous diseases such as sarcoidosis.[4] This chapter updates the main geoepidemiological features associated with sarcoidosis using the merged data of 117,175 patients with sarcoidosis included in large series (>100 patients) reported in the PubMed library.[5–103]

PREVALENCE AND INCIDENCE

Table 1.1 summarizes the prevalence and incidence rates of sarcoidosis country per country. The highest rates are reported in Northern Europe, the United States, and India (Fig. 1.1A and B): the estimated incidence in Europe ranges between 1 and 15 cases per 100,000 inhabitants, with significantly higher rates in northern countries.[104] In the United States, sarcoidosis is more common in Black/African Americans (BAAs).[105] In the largest reported US series,[56] the highest incidence rate was reported in BAA people (17.8 per 10^6 inhabitants) compared with Whites, Hispanics, and Asians (8.1, 4.3, and 3.2, respectively). In Detroit, Rybicki et al.[106] reported an incidence rate of 35.5 in BAA versus 10.9 in Whites, while two Navy studies[107,108] reported rates of 47.8–81.8 for BAA compared with 4.4–7.6 for Whites. Similar differences are reported for the prevalence per 100,000 inhabitants in US studies (64–141 for BAAs, 7–50 for Whites, 22 for Hispanics, and 19 for Asians).[56,109,110] Out of the United States, people from India living in London or Singapore had the highest rates of incidence and those from East Asia living in the United States or Singapore the lowest rates in comparison with the other ethnicities living in the same geographical area. In multiethnic cohorts from London, with a differing ethnic distribution than the US cohorts, the highest rates were reported in West Indian (incidence of 58, prevalence of 183 cases per 10^6 inhabitants) and Irish (incidence 21, prevalence 155) people in comparison with UK-born people (incidence 4, prevalence 27).[111,112] Benatar found a prevalence among Blacks of 23.2 per 10^6 inhabitants compared with Whites (3.7) and mixed race (11.6) [113] people in Cape Town, while Anantham et al.[114] reported a yearly incidence of 0.56 per 10^6 inhabitants in Singapore, with clearly different figures for Indian (4.57), Malaysian (1.30), and Chinese (0.23) people.

AGE AND GENDER

Our big data analysis confirmed that sarcoidosis affects both sexes but with a slight predominance of females and is mainly diagnosed in the fourth and fifth decades of life, with a mean age at diagnosis of 41 years and 52% of women affected in our merged data analysis (Table 1.2). Specific analysis of cohorts from the three main geographical areas (United States, Europe, and Asia) found significant differences, especially in

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TABLE 1.1
Worldwide Rates of Incidence and Prevalence of Sarcoidosis per 100,000 Inhabitants Ordered by Continent

First Author	Year	City/Region	Country	Incidence	Prevalence
Fletcher	1966	Kitwe	Zambia	3.1–9.7	NA
Lee	2002	Taiwan	China	NA	0.25
Wu	2016	Taiwan	China	NA	2.17
Gupta	1985	Delhi	India	NA	61.2
Gupta	1985	Calcutta	India	NA	150
Rakower	1964	–	Israel	0.5	1.6
Yigla	2006	Haifa	Israel	2	NA
Yigla	2002	Haifa	Israel	0.8	NA
Hasada	1972	–	Japan	NA	1–2
Hiraga	1974	–	Japan	1.7	NA
Hosoda & Nobechi	1964	–	Japan	NA	5.6
Hosoda	1980	–	Japan	0.5	NA
Morimoto	2008	–	Japan	1.01	NA
Nobechi	1964	Tokyo districts	Japan	0.3	NA
Pietinalho	2000	Hokkaido	Japan	1	3.7
Yamaguchi	1989	–	Japan	1.3	3
Kim	2001	Korea	Korea	0.125	NA
Al-Khouzaie	2011	Dhahran	Saudi Arabia	NA	13
Anantham	2007	Singapore	Singapore	0.56	NA
Gillman	2007	Geelong Victoria	Australia	4.4–6.3	NA
Heyworth	NA	Brisbane	Australia	10.1	NA
Marshman	1964	–	Australia	NA	9.2
Price	1980	Melbourne	Australia	8.35	NA
Reid	1964	Auckland	New Zealand	NA	6.13
Reid	1964	Wellington	New Zealand	NA	24.3
Reid	1964	Christchurch	New Zealand	NA	18.41
Thomeer	2001	Flanders	Belgium	0.26	1.94
Alilovic	2004	Croatia	Croatia	NA	4.1
Mise	2011	Split-Dalmatia County	Croatia	3.3	15.6
Kolek	1994	Moravia & Silesia	Czech	3.3–4.4	41.3–63.1
Levinsky	1964	–	Czechoslovakia	NA	10
Levinsky	1976	–	Czechoslovakia	2.3	NA
Alsbirk	1964	–	Denmark	3.4	NA
Alsbirk	1964	–	Denmark	8	NA
Byg	2003	–	Denmark	7.2	NA

TABLE 1.1
Worldwide Rates of Incidence and Prevalence of Sarcoidosis per 100,000 Inhabitants Ordered by Continent—cont'd

First Author	Year	City/Region	Country	Incidence	Prevalence
Horwitz	1964	–	Denmark	5.5	NA
Horwitz	1964	Copenhagen	Denmark	3	NA
Horwitz	1964	Zealand	Denmark	2–5.2	NA
Horwitz	1964	Bornholm	Denmark	4.1	NA
Horwitz	1964	Funen	Denmark	4–4.9	NA
Horwitz	1964	Jutland	Denmark	3.5–16.1	NA
Horwitz	1971	–	Denmark	14	NA
Horwitz	1971	–	Denmark	10.8	NA
Romer	1977	–	Denmark	5	NA
Selroos	1974	–	Denmark	9.2	NA
Patiala	1964	–	Finland	NA	8.1
Pietinalho	2000	Mjölbolsta hospital	Finland	11.4	28.2
Poukkula	1986	Northern Ostrobothnia	Finland	15	32
Riska	1964	–	Finland	NA	5.1
Selroos	1974	–	Finland	7.5	NA
Duchemann	2017	Seine-Saint Denis (Greater Paris)	France	4.9	30.2–44.78
Turiaf	1964	–	France	NA	5.2–10.1
Behrend	1974	Marburg	Germany	NA	50
Behrend	1974	Marburg Biedenkopf distrcit	Germany	NA	98
Buss	1975	–	Germany	28	NA
Fried	1964	West Berlin	Germany	NA	14.5
Lindig	1964	Leipzig	Germany	NA	13.3
Maike	2012	–	Germany	NA	32–69
Steinbruck & Zaumseil	1974	East germany	Germany	NA	31.3
Karakatsani	2009	–	Greece	1.07	5.89
Mandi	1964	Debrecen	Hungary	NA	4–5
Donnelly	2013	Count Offaly	Ireland	NA	85
Logan	1964	Dublin	Ireland	NA	33.3
Nicholson	2010	–	Ireland	NA	28.13
Beghe	2017	Parma province	Italy	NA	49
Blasi	1974	5 northern/4 southern cities	Italy	3	NA
Fazzi	1992	Tuscani	Italy	1.2	NA
Muratore	1964	Puglia and Lucania	Italy	1.2–2.5	NA

Continued

TABLE 1.1
Worldwide Rates of Incidence and Prevalence of Sarcoidosis per 100,000 Inhabitants Ordered by Continent—cont'd

First Author	Year	City/Region	Country	Incidence	Prevalence
Orie	1964	–	Netherlands	21.6	NA
Riddervold	1964	–	Norway	14.4	26.7
Jaroszewicz	1964	Warsaw	Poland	NA	6.9
Jaroszewicz	1977	–	Poland	7.7	10.7
Kowalska	2014	Silesian voivodeship	Poland	3.8–4.5	NA
Villar	1964	–	Portugal	NA	0.2
Centea	1964	Nortwestern region	Romania	NA	3.3
Rabuchin	1975	Leningrad	Russia	NA	2.3
Rabuchin	1975	Moscow	Russia	NA	1.1
Rabuchin	1975	Talin	Russia	NA	3.8
Rabuchin	1975	Riga	Russia	NA	2.1
Denic-Markovic	NA	–	Serbia	NA	16.5
Pesut	2005	Serbia/Montenegro	Serbia	1.9	NA
Virsik	1974	West Slovakia	Slovakia	1	9.6
La Grasta	1964	Slovenia	Slovenia	NA	11.9
Alcoba Leza	2003	Leon	Spain	1.37	NA
Maña	1992	Barcelona	Spain	1.36	NA
Siso	2017	Catalonia	Spain	NA	25
Arkema	2016	–	Sweden	11.5	160
Bauer	1964	–	Sweden	NA	55
Bauer	1964	–	Sweden	NA	64
Hillerdal	1984	Uppsala	Sweden	14.7–23.2	NA
Wallgren	1958	–	Sweden	NA	42
Deubelbeiss	2010	–	Switzerland	7	121
Pohle	2016	–	Switzerland	NA	53.66
Sommer	1964	–	Switzerland	NA	16.3
BTTA	1969	–	UK	3.25	NA
Douglas	1964	Scotland	UK	NA	5–12
Douglas	1964	–	UK	NA	3–7
Douglas	1964	–	UK	NA	20–25
Douglas	1964	–	UK	NA	5.5–13.4
Gribbin	2006	–	UK	5	NA
James	1964	Britain	UK	NA	20
James	1964	London	UK	NA	19
Milliken	1964	North Ireland	UK	10.3	NA
Nicholson	2010	North Ireland	UK	NA	11.16

TABLE 1.1
Worldwide Rates of Incidence and Prevalence of Sarcoidosis per 100,000 Inhabitants Ordered by Continent—cont'd

First Author	Year	City/Region	Country	Incidence	Prevalence
Parkes	1985	Isle of Man	UK	14.7	NA
Parkes	1985	Isle of Man	UK	3.5	NA
Sutherland	1965	–	UK	8.3	NA
Pollak	1964	–	Canada	NA	10.5
Baughman	2016	–	US	8	60
Cragin	2009	Vermont state	US	NA	66.1
Gundelfinger	1961	–	US	NA	NA
Henke	1986	Rochester, MN	US	6.1	NA
Reich	1996	Northwest Region	US	4.8	NA
Robins	1964	New York	US	NA	39
Ungprasert	2016	Olmsted County, Minnesota	US	10	NA
Castells	1964	–	Argentina	NA	1
Purriel	1961	Buenos Aires	Argentina	1.3–2.4	NA
Rey	1964	–	Argentina	NA	5
Bethlem	1985	–	Brazil	NA	10
Certain & De Paula	1964	–	Brazil	NA	0.2
Coquart	2015	–	Guadeloupe Islands	2.28	21.09
Purriel	1961	–	Uruguay	0.4	NA

gender distribution (Fig. 1.2): the highest percentage of females was reported in Asian studies (65%) and the lowest in European (49%), while the youngest age at diagnosis was found in the US studies (39.8 years).

Ethnicity may influence the mean age at diagnosis and the gender ratio, as has been reported by US studies in BAA patients,[56] who developed the first sarcoidosis-related symptoms at an earlier age than Whites.[49,115] A classification of the reported cohorts according to the predominant ethnicity (>50%) found that the frequency of women affected was significantly higher in predominantly BAA cohorts than in Asian and White predominant cohorts (67% vs. 64% vs. 51%, respectively, $P < .001$) (Fig. 1.3); the higher the frequency of BAA patients included in a cohort, the greater the number of females, while the higher the frequency of White patients, the higher the number of males. A geographical gradient for the gender ratio is observed in studies from countries located between parallels 30 and 45 (Mediterranean countries, Japan, and Southern United States), in which two-thirds of patients with sarcoidosis are women, while in the north of Europe and India more than half the patients are men.

ETHNICITY

Although sarcoidosis affects all ethnicities, it is more frequently reported in Whites. According to our big data, ethnicity was detailed in 25,951 patients: 15,443 (59.5%) were classified as White, 6520 (25.1%) as BAA, 2985 (11.5%) as Asian, and 1003 (3.9%) as other ethnicities (Table 1.2) (Fig. 1.4). There are large ethnicity-driven variations in the frequency, epidemiological and clinical expression, and outcomes, although the differences should be always evaluated taking into account socioeconomic disparities that could modify the level of exposure to potential environmental toxins.[104]

How Ethnicity Influences the Clinical Presentation

The differing clinical expression of sarcoidosis according to ethnicity was first reported in the 1960s.[116,117] Most recent studies have been carried out in multiethnic populations and have reported a differing clinical expression when comparing between different ethnicities. The largest US studies comparing the two predominant ethnicities (BAAs vs. Whites) reported a higher frequency of advanced radiographic stages of sarcoidosis, low FVC% predictive values, and more organs involved in BAA patients, including a higher frequency of ocular, liver, bone marrow, extrathoracic lymph nodes, and skin (other than erythema nodosum) sarcoidosis, while splenic involvement and hypercalcemia were more frequent in Whites. In addition, BAA patients

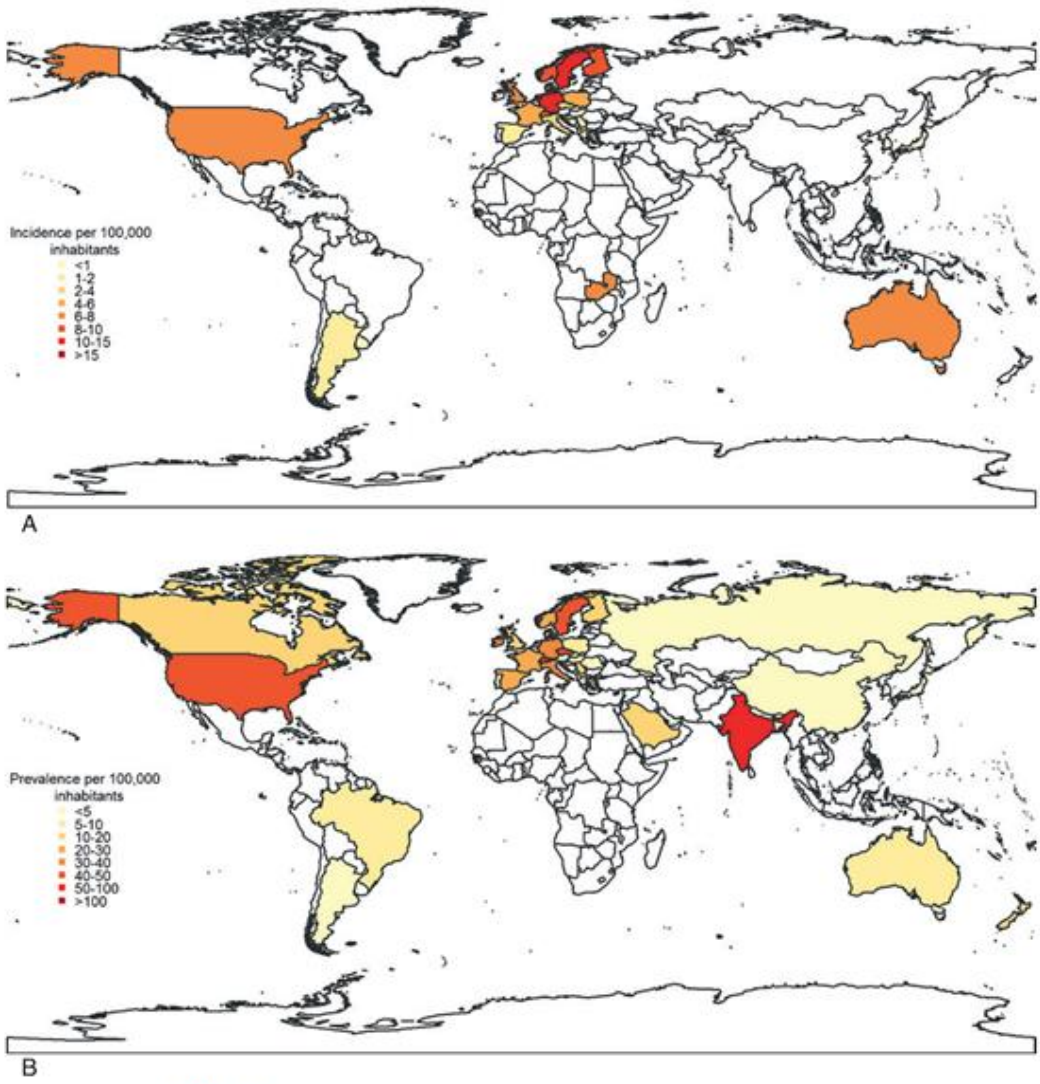

FIG. 1.1 Worldwide frequency of sarcoidosis: **(A)** incidence and **(B)** prevalence.